REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary correctly indicates that claims 143-162 are pending in the application, are under consideration and stand rejected.

Claim 155 has been amended to correct an obvious typographical error.

Claims 148, 155, 157, 160 and 161 been amended to more clearly describe the claimed subject matter. Support for the amendments can be found throughout the specification and claims as originally filed.

Claims 162 and 163 are added. Support for these claims can be found as previously described for claims 155 and 161.

No prohibited new matter has been introduced by way of the above amendments. Applicants reserve the right to file a continuation or divisional application on subject matter canceled by way of this Amendment.

Objections

Claim 155 was objected to for containing a typographical error. The error has been corrected.

Rejections under 35 U.S.C. § 112

Claims 155-157, 160 and 161 stand rejected under 35 U.S.C. § 112 for allegedly failing to comply with the written description requirement. Specifically, the Office has noted that these claims rely upon cells that are identified according to the method of claim 148, and has alleged that, because the cells relied upon in these claims have allegedly not yet been identified, the specification cannot have described any product made by using these cells or any method that uses these cells for further process steps. The rejection is respectfully traversed.

Claim 148 defines a process of manufacture. Claim 155 is directed to an extension of that method which takes the product of claim 148 as an intermediate material and produces another material. In making this rejection, the Office implies that no process of manufacture

can ever be sufficiently described if the process comprises the production of an intermediate material. This cannot be so.

The Office has correctly acknowledged that the method of claim 148 is fully described. Although, such an amendment is not necessary to overcome the rejection, claim 148 has been amended to recite that the final step is isolating the recited cells. The amendment serves to emphasize that the method of claim 148 is a method of manufacturing a product and not simply a research method of identifying cells.

Thus, the cells isolated according to claim 148 represent a product defined by the process used to make them. This process necessarily produces isolated cells having the features recited in claim 148. Claim 157 is a product-by-process claim directed to a composition comprising such cells. Claim 155 and the claims that depend from claim 155 simply utilize the product according to claim 148 in further processing steps that result in a further related product that is, itself, defined by the process used to make it. Claim 161 is directed to a composition comprising the product of claim 155.

Product by process claims are proper under 35 U.S.C. § 112. *See, e.g.,* M.P.E.P. § 2173.05(p); *see also, In re Luck*, 476 F.2d 650, 177 USPQ 523 (CCPA 1973); *In re Pilkington*, 411 F.2d 1345, 162 USPQ 145 (CCPA 1969); *In re Steppan*, 394 F.2d 1013, 156 USPQ 143 (CCPA 1967). It is long established that a product may be adequately described as required under 35 U.S.C. § 112, by the method in which it is made. Method claims that recite the use of such products can be no less adequately described than method claims that take one material and make another.

Working examples of claims 155-157, 160 and 161, as well as the related claim 148 are provided by Example 4 in the specification. B6 spleen cells were stimulated with TAP-/- and RMA-S.B7-1 cells. TAP was directly ablated by knocking out gene expression in two independent ways. This stimulation of B6 cells reproducibly resulted in cytotoxic responses against RMA-S and TAP -/- targets. This demonstrates conclusively that it is not reactions to TAP inhibitor molecular compositions *per se* or any unforeseen or impurity components that artificially constitute the antigens. Rather, the example demonstrates that the response is only due to the novel endogenous self-antigen changes being expressed on the cells that have their TAP function altered. The reproducibility of the stimulation described in the example demonstrates that the claimed methods predictably produce cells having the recited properties.

Moreover, the cells isolated by the method of claim 148 have distinctive properties that are described in claim 148 by their selective recognition of specific cells. This is analogous to the manner in which antibodies are described, which has been accepted by the Federal Circuit as adequate. Claims to antibodies, including those yet to be isolated, are held to be adequately described if the corresponding antigen is fully described. *See, Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir 2004). The antibodies are defined by functional properties, which are a result of the process by which they are made. Here, the cells isolated by the method of claim 148 are described both in terms of the method of making the cells and by the selective recognition properties of the cells.

By the present amendment, claim 163 is added to recite the subject matter of claim 155 in the form a method according to claim 148 further comprising additional steps and resulting in the isolation of cells. New claim 164 is directed to a composition comprising the cells isolated by the method of claim 163. These claims are added to illustrate that, since claim 148 is fully described, claim 155 cannot be any less adequately described simply because claim 155 takes an intermediate produced by the steps of claim 148 as a starting material. And, as the method of making the cells is fully described, the product of that process must likewise be adequately described, as has been long recognized by the Office.

For at least the forgoing reasons, the rejection should be withdrawn and such action is respectfully requested.

Rejections under 35 U.S.C. § 102

A. Nair et al.

Claims 143-147, 159 and 162 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Nair et al. (U.S. 5,831,068). The rejection is respectfully traversed.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

Claim 143 recites a method for impairing cellular peptide processing for MHC presentation comprising treating cells with a substance wherein the substance is characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC class I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule B7-1; and thereby inducing immunological effector cells specific for **endogenous** epitopes associated with impaired cellular peptide processing for MHC presentation.

Nair et al. teaches a method for presenting an antigen in the form of a peptide on the surface of a cell. The method involves inhibiting the activity of an MHC class I pathway-associated component (e.g., a TAP protein or a proteasome or its components) in a cell and contacting the cell with an antigenic peptide to produce a potent antigen presenting cell. *See*, Nair et al. at abstract. That is, Nair et al. teaches a way to present an **exogenous** antigen on the surface of a cell to make an antigen presenting cell. Part of the process taught by Nair et al. includes inhibiting a TAP protein. Nair et al. teaches that this makes the cells deficient in endogenous peptide loading. Contacting the cell with an exogenous results in loading of the empty class I molecules as a mean of forcing the **exogenous** peptide to be displayed as an antigen. See, Nair et al at col. 2, ll. 43-50.

Nair et al. does not teach or suggest a method that results in specific lysis by CTL elicited by **endogenous** MHC class I dependent antigens of the TAP-deficient variant. The present inventors have invented methods that provide effector cells capable of recognizing the specific endogenous signature of cells having impaired processing. The method of claim 143 produces immunological effectors cells that are specific for **endogenous** epitopes associated with impaired cellular peptide processing for MHC presentation. Nair et al. teaches no such effector cells, nor any method of inducing such cells. Indeed, the Office has acknowledged that Nair et al. do not teach a method that results in specific lysis by CTL elicited by **endogenous** MHC class I dependent antigens of the TAP-deficient variant, because Nair et al. exposes cells to exogenous peptides. See, Office Action at 8.

With respect to claim 159, Nair et al. does not teach a composition comprising a substance that impairs peptide processing for MHC presentation in combination with and adjuvant. The difference between the composition taught by Nair et al. is due to the different intended uses of the compostion. Nair et al. teaches the use of a lipid transfection agent for the introduction of a retroviral vector. See, Nair et al at col. 8, ll. 38-41. The Office has

asserted that the lipid taught by Nair et al. as a transfection agent meets the limitation of the adjuvant in claim 159. However, Nair et al. does not teach or suggest liposomes that are adjuvants as recited in claim 159. In immunology, adjuvants are defined as "a substance capable of enhancing an immune response to an antigen." Academic Press Dictionary of Science and Technology 46 (Christopher Morris ed., 1991). Liposomal adjuvants have particular properties that would not be expected to be useful in a transfection reagent as taught by Nair et al. *See, e.g.,* Carl Alving, Liposomes as Carriers of Vaccines in Liposomes From Biophysics to Therapeutics 210-2 (Marc Ostro ed., Marcel Dekker, Inc., 1987). Unless specifically intended for use in a vaccine, a lipid transfection agent would not generally contain lipids that would induce an immune response.

It is clear that Nair et al. fails to teach or suggest anything like the claimed invention, let alone teach the identical invention in as complete detail as is contained in the claims as required for the reference to anticipate the present claims. For at least the foregoing reasons, withdrawal of the rejection is respectfully requested.

B. Hammond et al.

Claims 155-157, 160 and 161 have been rejected as allegedly anticipated by Hammond et al. (Nature, 364:158-61, 1993). The rejection is respectfully traversed.

Hammond concerns the recognition of HIV antigens by CTL. In most cases, antigen presentation involves TAP proteins. Hammond et al. show that the HIV env protein is processed by a TAP independent pathway. Like Nair et al., Hammond is concerned with the presentation of **exogenous** antigens. The use of TAP independent pathways for the presentation of the exogenous antigens is different from the presently claimed methods that produce cells capable of identifying TAP impaired cells based on their endogenous antigen signatures. The product of Hammond's methods are cells that recognize the HIV env antigen, not cells that specifically recognize **endogenous** epitopes associated with impaired peptide processing for MHC class I presentation.

Hammond et al. does not teach or suggest isolating cells that activate CD8+ T lymphocytes that selectively recognize cells showing **endogenous** epitopes associated with impaired cellular peptide processing for MHC presentation as recited in claim 148, from which claim 155 depends. Hammond et al. does not teach or suggest using such cells in a method as recited in claim 155 that results in isolating immunological effector cells that

selectively recognize cells showing impaired cellular peptide processing for MHC presentation, and Hammond et al certainly does not teach isolated effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation.

For at least the forgoing reasons, Hammond et al. fails to anticipate the claimed invention. Withdrawal of the rejection is respectfully requested.

C. Wolpert et al.

Claims 155-157, 160 and 161 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Wolpert et al. (PNAS, 94:11496-11501, Oct 1997). The publication of this reference occurred after the priority date of the present application. The Office has asserted that the foreign priority papers cannot be relied upon to overcome this rejection because a translation of said papers has not been made of record. Applicant's note that the original priority document was filed in the English language. A copy of the priority application in the English language is attached. A certified copy of this document has also been ordered and will be submitted as soon as it can be acquired.

Applicants are entitled to the benefit of SE 9604581-0, filed December 12, 1996. Therefore, the reference does not constitute prior art. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 148-158, 160 and 161 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over Nair et al., supra, in view of Sandberg et al. (Eur Journal of Immunology, 26:288-93, 1996) and Skipper et al. (J. Experimental Medicine, 183:527-34, 1996).

The prior art fails to establish a proper prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

It is impermissible to first ascertain factually what applicants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct applicant's invention from such prior art. *See, e.g., Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 550 (Fed. Cir. 1985); *see also, In re Shuman*, 150 U.S.P.Q. 54, 57 (C.C.P.A 1966). In asserting this rejection, the Office has taken a primary reference that is directed to very distinct subject matter, and using impermissible hindsight, selectively picked secondary references that are purported to teach one individual modification or another in an attempt to reconstruct the presently claimed invention. However, the secondary references themselves show that there would have been no motivation, and no reasonable expectation of success, to combine the secondary references as proposed by the Office.

Moreover, the results sought and obtained in each of the references is distinct, if not opposite, to the presently claimed invention. An analysis of obviousness of a claimed combination must include consideration of the results achieved by that combination. *The Gillette Co. v. S.C. Johnson & Son Inc.,* 16 USPQ2d 1923, 1928 (Fed. Cir. 1990). Critical to the analysis is an understanding of the particular results achieved by the new combination. *Id.* (citing *Interconnect Planning Corporation v. Feil,* 227 U.S.P.Q. 543, 551 (Fed. Cir 1985)). Therefore, the references could not be combined to arrive at the present invention even if all the elements of the invention could be discerned in the combined references.

The deficiencies of Nair et al. are addressed above. The teachings of Nair et al. are entirely unrelated to the present invention, because Nair et al. is directed to a method of short-circuiting the MHC class I presentation pathway and inserting exogenous peptides in place of the peptides that would otherwise be presented.

Sandberg et al is concerned with the question: Is there any diversity and specificity at all in the very few total number of cells in the adaptive cellular immune system in immune dysfunctional TAP-/- individuals? The answer obtained by Sandeberg et al. is yes, even in immune dysfunctional TAP-/- individuals some diversity and peptide specificity do exist.

This indicated that positive thymus selection of an apparently diverse CD8+ T cell repertoire can occur in the presence of only the limited set of TAP-independent peptides. However, Sandberg et al did not contradict earlier findings that it is very inefficient with very few such cells in total number (ref 19, in the Sandberg et al paper).

The question raised and experiment set up is almost exactly opposite to the purpose and teaching of the present application and the results obtained are also the opposite. In Sandberg et al., when immune dysfunctional TAP-/- effector cells were stimulated with normal non-dysfunctional TAP+/+ cells it yielded cells very potent in killing RMA (TAP+/+) but not in killing RMA-S (TAP-/-). (See Table 1: TAP-/- anti B6)

The method of Sandberg et al. did not produce cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation as recited in claim 148. By contrast, in the present application, when normal immune functional TAP+/+ effector cells are stimulated with non-normal dysfunctional TAP-/- cells. it yields cells that do not target RMA (TAP+/+) but very potently and specifically kill RMA-S (TAP-/-) cells. *See e.g.*, Specification at Fig5A: B6 anti TAP-/-.

Where, as here, the purpose and result of a cited reference is entirely opposed to the claimed invention there can be no motivation to modify or combine that reference to arrive at the claimed invention.

Skipper et al. bears almost no discernable relationship to the presently claimed invention or to Sandberg et al. or to Nair et al. The Office alleges that Skipper et al. teaches a peptide that is recognized by a CTL clone that can recognize the tryrosine kinase gene product on melanoma cells. Skipper et al. hypothesize that a posttranslational conversion of asparagine to aspartic acid provides for processing through the ER. Skipper et al. found these peptides by proteomic methods. Skipper et al. does not teach or suggest any method of treating cells to isolate cells as described in the present claims. Sandberg et al. clearly fails to cure the deficiencies of Nair et al. and Sanderg et al.

In view of the foregoing, the cited references clearly fail to make out a prima facie case of obviousness. The combination neither teaches all the elements of the claimed invention nor provides any motivation to combine or modify the references as proposed. Furthermore, there is no data presented in any of the cited art that would lead a person of ordinary skill in the art to have a reasonable expectation of success in making and practicing the presently claimed invention. For at least these reasons, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

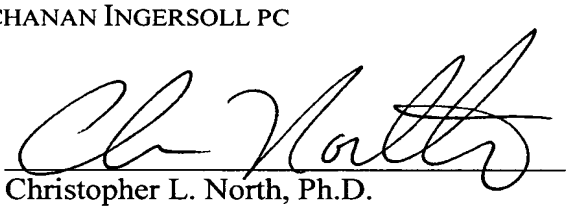
In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL PC

Date: February 15, 2006

By: 

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